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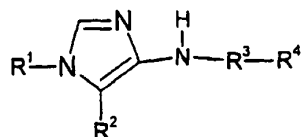
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(54) Title: IMIDAZOLE DERIVATIVES



(1)

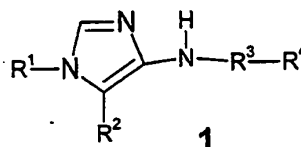
(57) Abstract: The invention provides compounds of formula (1),
wherein R¹, R², R³, and R⁴ are as defined, and their pharmaceutically
acceptable salts. Compounds of formula (1) are indicated to have
activity inhibiting cdk5, cdk2, and GSK-3. Pharmaceutical compositions
and methods comprising compounds of formula (1) for treating and
preventing diseases and conditions comprising abnormal cell growth,
such as cancer, and neurodegenerative diseases and conditions and
those affected by dopamine neurotransmission. Also described arepharmaceutical compositions and methods comprising compounds of formula (1) for treating male fertility and sperm motility;
diabetes mellitus; impaired glucose tolerance; metabolic syndrome or syndrome X; polycystic ovary syndrome; adipogenesis and
obesity; myogenesis and frailty, for example age-related decline in physical performance; acute sarcopenia, for example muscle
atrophy and/or cachexia associated with burns, bed rest, limb immobilization, or major thoracic, abdominal, and/or orthopedic
surgery; sepsis; hair loss, hair thinning, and balding; and immunodeficiency.

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CLAIMS

What is claimed is:

1. A compound of the formula



wherein R¹ is a straight chain or branched (C₁-C₈)alkyl, a straight chain or branched (C₂-C₈)alkenyl, a straight chain or branched (C₂-C₈)alkynyl, (C₃-C₈)cycloalkyl, (C₄-C₈)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C₅-C₁₁)bicycloalkyl, (C₇-C₁₁)bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C₆-C₁₄)aryl, or (5-14 membered) heteroaryl; and wherein R¹ is optionally substituted with from one to six substituents R⁵ independently selected from F, Cl, Br, I, nitro, cyano, -CF₃, -NR⁷R⁸, -NR⁷C(=O)R⁸, -NR⁷C(=O)OR⁸, -NR⁷C(=O)NR⁸R⁹, -NR⁷S(=O)₂R⁸, -NR⁷S(=O)₂NR⁸R⁹, -OR⁷, -OC(=O)R⁷, -OC(=O)OR⁷, -C(=O)OR⁷, -C(=O)R⁷, -C(=O)NR⁷R⁸, -OC(=O)NR⁷R⁸, -OC(=O)SR⁷, -SR⁷, -S(=O)R⁷, -S(=O)₂R⁷, -S(=O)₂NR⁷R⁸, -O-S(=O)₂R⁷, -N₃, and R⁷;

R² is H, F, -CH₃, -CN, or -C(=O)OR⁷;

R³ is -C(=O)NR⁸, -C(=O)O-, -C(=O)(CR¹⁰R¹¹)_n-, or -(CR¹⁰R¹¹)_n-;

R⁴ is a straight chain or a branched (C₁-C₈)alkyl, a straight chain or a branched (C₂-C₈)alkenyl, a straight chain or branched (C₂-C₈)alkynyl, (C₃-C₈)cycloalkyl, (C₄-C₈)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C₅-C₁₁)bicycloalkyl, (C₇-C₁₁)bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C₆-C₁₄)aryl, or (5-14 membered) heteroaryl; and wherein R⁴ is optionally substituted with from one to three substituents R⁶ independently selected from F, Cl, Br, I, nitro, cyano, -CF₃, -NR⁷R⁸, -NR⁷C(=O)R⁸, -NR⁷C(=O)OR⁸, -NR⁷C(=O)NR⁸R⁹, -NR⁷S(=O)₂R⁸, -NR⁷S(=O)₂NR⁸R⁹, -OR⁷, -OC(=O)R⁷, -OC(=O)OR⁷, -C(=O)OR⁷, -C(=O)R⁷, -C(=O)NR⁷R⁸, -OC(=O)NR⁷R⁸, -OC(=O)SR⁷, -SR⁷, -S(=O)R⁷, -S(=O)₂R⁷, -S(=O)₂NR⁷R⁸, or R⁷;

each R⁷, R⁸, and R⁹ is independently selected from H, straight chain or branched (C₁-C₈)alkyl, straight chain or branched (C₂-C₈)alkenyl, straight chain or branched (C₂-C₈)alkynyl, (C₃-C₈)cycloalkyl, (C₄-C₈)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C₅-C₁₁)bicycloalkyl, (C₇-C₁₁)bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C₆-C₁₄)aryl, and (5-14 membered) heteroaryl, wherein R⁷, R⁸, and R⁹ are each independently optionally substituted with from one to six substituents independently selected from F, Cl, Br, I, NO₂, -CN, -CF₃, -NR¹⁰R¹¹, -NR¹⁰C(=O)R¹¹, -NR¹⁰C(=O)OR¹¹, -NR¹⁰C(=O)NR¹¹R¹², -NR¹⁰S(=O)₂R¹¹, -NR¹⁰S(=O)₂NR¹¹R¹²,

$-\text{OR}^{10}$, $-\text{OC}(=\text{O})\text{R}^{10}$, $-\text{OC}(=\text{O})\text{OR}^{10}$, $-\text{OC}(=\text{O})\text{NR}^{10}\text{R}^{11}$, $-\text{OC}(=\text{O})\text{SR}^{10}$, $-\text{SR}^{10}$, $-\text{S}(=\text{O})\text{R}^{10}$, $-\text{S}(=\text{O})_2\text{R}^{10}$, $-\text{S}(=\text{O})_2\text{NR}^{10}\text{R}^{11}$, $-\text{C}(=\text{O})\text{R}^{10}$, $-\text{C}(=\text{O})\text{OR}^{10}$, $-\text{C}(=\text{O})\text{NR}^{10}\text{R}^{11}$, and R^{10} ;

or, when R^7 and R^8 are as in NR^7R^8 , they may instead optionally be connected to form with the nitrogen of NR^7R^8 to which they are attached a heterocycloalkyl moiety of from three to seven ring members, said heterocycloalkyl moiety optionally comprising one or two further heteroatoms independently selected from N, O, and S;

each R^{10} , R^{11} , and R^{12} is independently selected from H, straight chain or branched (C_1 - C_8)alkyl, straight chain or branched (C_2 - C_8)alkenyl, straight chain or branched (C_2 - C_8 alkynyl), (C_3 - C_8)cycloalkyl, (C_4 - C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5 - C_{11})bicycloalkyl, (C_7 - C_{11})bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C_6 - C_{14})aryl, and (5-14 membered) heteroaryl, wherein R^{10} , R^{11} , and R^{12} are each independently optionally substituted with from one to six substituents independently selected from F, Cl, Br, I, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{NR}^{13}\text{C}(=\text{O})\text{R}^{14}$, $-\text{NR}^{13}\text{C}(=\text{O})\text{OR}^{14}$, $-\text{NR}^{13}\text{C}(=\text{O})\text{NR}^{14}\text{R}^{15}$, $-\text{NR}^{13}\text{S}(=\text{O})_2\text{R}^{14}$, $-\text{NR}^{13}\text{S}(=\text{O})_2\text{NR}^{14}\text{R}^{15}$, $-\text{OR}^{13}$, $-\text{OC}(=\text{O})\text{R}^{13}$, $-\text{OC}(=\text{O})\text{OR}^{13}$, $-\text{OC}(=\text{O})\text{NR}^{13}\text{R}^{14}$, $-\text{OC}(=\text{O})\text{SR}^{13}$, $-\text{SR}^{13}$, $-\text{S}(=\text{O})\text{R}^{13}$, $-\text{S}(=\text{O})_2\text{R}^{13}$, $-\text{S}(=\text{O})_2\text{NR}^{13}\text{R}^{14}$, $-\text{C}(=\text{O})\text{R}^{13}$, $-\text{C}(=\text{O})\text{OR}^{13}$, $-\text{C}(=\text{O})\text{NR}^{13}\text{R}^{14}$, and R^{13} ;

each R^{13} , R^{14} , and R^{15} is independently selected from H, straight chain or branched (C_1 - C_8)alkyl, straight chain or branched (C_2 - C_8)alkenyl, straight chain or branched (C_2 - C_8 alkynyl), (C_3 - C_8)cycloalkyl, (C_4 - C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5 - C_{11})bicycloalkyl, (C_7 - C_{11})bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C_6 - C_{14})aryl, and (5-14 membered) heteroaryl, wherein R^{13} , R^{14} , and R^{15} are each independently optionally substituted with from one to six substituents independently selected from F, Cl, Br, I, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, $-\text{NR}^{16}\text{R}^{17}$, $-\text{NR}^{16}\text{C}(=\text{O})\text{R}^{17}$, $-\text{NR}^{16}\text{C}(=\text{O})\text{OR}^{17}$, $-\text{NR}^{16}\text{C}(=\text{O})\text{NR}^{17}\text{R}^{18}$, $-\text{NR}^{16}\text{S}(=\text{O})_2\text{R}^{17}$, $-\text{NR}^{16}\text{S}(=\text{O})_2\text{NR}^{17}\text{R}^{18}$, $-\text{OR}^{16}$, $-\text{OC}(=\text{O})\text{R}^{16}$, $-\text{OC}(=\text{O})\text{OR}^{16}$, $-\text{OC}(=\text{O})\text{NR}^{16}\text{R}^{17}$, $-\text{OC}(=\text{O})\text{SR}^{16}$, $-\text{SR}^{16}$, $-\text{S}(=\text{O})\text{R}^{16}$, $-\text{S}(=\text{O})_2\text{R}^{16}$, $-\text{S}(=\text{O})_2\text{NR}^{16}\text{R}^{17}$, $-\text{C}(=\text{O})\text{R}^{16}$, $-\text{C}(=\text{O})\text{OR}^{16}$, $-\text{C}(=\text{O})\text{NR}^{16}\text{R}^{17}$, and R^{16} ;

each R^{16} , R^{17} , and R^{18} is independently selected from H, straight chain or branched (C_1 - C_8)alkyl, straight chain or branched (C_2 - C_8)alkenyl, straight chain or branched (C_2 - C_8 alkynyl), (C_3 - C_8)cycloalkyl, (C_4 - C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5 - C_{11})bicycloalkyl, (C_7 - C_{11})bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C_6 - C_{13})aryl, and (5-12 membered) heteroaryl;

n is 0, 1, 2, or 3;

wherein R^{10} and R^{11} in $-\text{C}(=\text{O})(\text{CR}^{10}\text{R}^{11})_n-$ and $-(\text{CR}^{10}\text{R}^{11})_n-$ are for each iteration of n defined independently as recited above;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein R^3 is $-\text{C}(=\text{O})\text{NH}-$ or $-\text{C}(=\text{O})(\text{CR}^{10}\text{R}^{11})_n-$.

3. A compound according to claim 1, wherein R¹ is optionally substituted (C₃-C₈)cycloalkyl or optionally substituted (C₅-C₁₁) bicycloalkyl.

4. A compound according to claim 4, wherein R¹ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, or bicyclo-[3.1.0]-hexyl, each optionally substituted.

5. A compound according to claim 1, wherein R¹ is optionally substituted straight chain or branched (C₁-C₈)alkyl or optionally substituted straight chain or branched (C₂-C₈)alkenyl.

6. A compound according to claim 1, wherein R⁴ is (C₆-C₁₄)aryl or (5-14 membered) heteroaryl, each optionally substituted.

7. A compound according to claim 6, wherein R⁴ is phenyl, pyridyl, naphthyl, quinolyl, or isoquinolyl, each optionally substituted.

8. A compound according to any of claims 1-7, wherein R² is hydrogen.

9. A compound of claim 1, selected from the group consisting of:

15 *N*-(1-cyclobutyl-1H-imidazol-4-yl)-2-quinolin-6-yl-acetamide;
N-(1-cyclopentyl-1H-imidazol-4-yl)-2-(4-methoxy-phenyl)-acetamide;
N-[1-(*cis*-3-phenyl-cyclobutyl)-1H-imidazol-4-yl]-2-quinolin-6-yl-acetamide;
 (1-cyclobutyl-1H-imidazol-4-yl)-carbamic acid phenyl ester;
 1-(1-cyclobutyl-1H-imidazol-4-yl)-3-isoquinolin-5-yl-urea;
 20 *N*-[1-(*cis*-3-amino-cyclobutyl)-1H-imidazol-4-yl]-2-naphthalen-1-yl-acetamide;
 6-methyl-pyridine-2-carboxylic acid {*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-amide;
 1H-imidazole-4-carboxylic acid {*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-amide;
 25 6-hydroxy-pyridine-2-carboxylic acid {*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-amide;
 3-methyl-pyridine-2-carboxylic acid {*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-amide;
 2-pyridin-3-yl-thiazole-4-carboxylic acid {*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-amide;
 30 6-{*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutylcarbonyl}-nicotinic acid methyl ester;
 pyrazine-2-carboxylic acid {*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-amide;
 35 *N*-(*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl)-benzamide;

- 5-methyl-pyrazine-2-carboxylic acid {*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-amide;
 N-{*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-isobutyramide;
 6-chloro-pyridine-2-carboxylic acid {*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-amide;
 5 quinoline-2-carboxylic acid {*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-amide;
 1H-pyrrole-2-carboxylic acid {*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-amide;
 10 N-{*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-2-m-tolyl-acetamide;
 pyridine-2-carboxylic acid {*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-amide;
 2-(3-hydroxy-phenyl)-N-{*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-acetamide;
 15 piperidine-4-carboxylic acid {*cis*-3-[4-(2-naphthalen-1-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-amide hydrochloride;
 N-[1-(*cis*-3-acetylamino-cyclobutyl)-1H-imidazol-4-yl]-2-naphthalen-2-yl-acetamide;
 N-{*cis*-3-[4-(2-isoquinolin-5-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-benzamide; and
 20 pyridine-2-carboxylic acid {*cis*-3-[4-(2-isoquinolin-5-yl-acetylamino)-imidazol-1-yl]-cyclobutyl}-amide; and
 pharmaceutically acceptable salts of the foregoing compounds.

10. A pharmaceutical composition for treating a disease or condition comprising abnormal cell growth or a neurodegenerative disease or condition in a mammal comprising a compound of claim 1 in an amount effective in treating said disease or condition, and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition for treating a disease or condition in a mammal the treatment of which can be effected or facilitated by altering dopamine mediated neurotransmission comprising a cdk5 inhibitor in an amount effective in treating said disease or condition or in an amount effective to inhibit cdk5 activity, and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition for treating in a mammal a disease or condition selected from male fertility and sperm motility; diabetes mellitus; impaired glucose tolerance; metabolic syndrome or syndrome X; polycystic ovary syndrome; adipogenesis and obesity; myogenesis and frailty, for example age-related decline in physical performance; acute sarcopenia, for example muscle atrophy and/or cachexia associated with burns, bed

rest, limb immobilization, or major thoracic, abdominal, and/or orthopedic surgery; sepsis; hair loss, hair thinning, and balding; and immunodeficiency, comprising a compound of claim 1 in an amount effective in treating said disease or condition, and a pharmaceutically acceptable carrier.

- 5 13. A pharmaceutical composition comprising a cdk5 inhibitor and a second member selected from the group consisting of an SSRI, an NK-1 receptor antagonist, a 5HT_{1D} antagonist, ziprasidone, olanzapine, risperidone, L-745870, sonepiprazole, RP 62203, NGD 941, balaperidone, flesinoxan, gepirone, an acetylcholinesterase inhibitor, TPA, NIF, a potassium channel modulator such as BMS-204352, and an NMDA receptor antagonist, 10 wherein the cdk5 inhibitor and the second member are together in an effective amount, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 01/01335

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D233/88 C07D401/12 C07D233/92 C07D403/12 C07D417/14
 C07D401/14 A61K31/4164 A61K31/4178 A61K31/455 A61K31/4709
 A61K31/4725 A61P35/00 A61P15/00 A61P25/00 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP 0 898 963 A (LILLY CO ELI) 3 March 1999 (1999-03-03) page 10, formula IB; page 15, formulas Ia, Ia'; page 22, scheme 6; pages 33-58, examples 1, 9 to 12; pages 73-297, examples 5, 8, 9-11, 13, 19, 20, 22, 25, 26, 31, 34 to 36, 39 to 41, 44, 49, 51, 54, 55, 58, 65, 67, 73, 80, 81, 85-96, 101, 102, 104, 105, 146, 153 to 164, 165-169, 172, 173, 175, 176 to 180, 187, 189, 195, 197 to 202, 205 to 216, 220, 221, 228, 230 to 233; pages 382, 383; page 22, line 35 to page 24, line 10</p> <p style="text-align: center;">--- -/-</p>	1-8, 10, 12



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

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P document published prior to the international filing date but later than the priority date claimed

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a document member of the same patent family

Date of the actual completion of the international search

13 December 2001

Date of mailing of the international search report

27/12/2001

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/IB 01/01335

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 933 365 A (LILLY CO ELI) 4 August 1999 (1999-08-04) page 7, formula IB; page 8, formula Ia'; page 16, formulas Ia, Ia'; page 23, scheme VI; pages 33-58, examples 1, 9 to 12; pages 77-180, examples 8 to 11, 13, 19, 20, 22, 25, 26, 31, 34 to 36, 39 to 41, 44, 49, 51, 55, 58, 65, 67, 73, 80, 81, 85 to 96, 101, 102, 104, 105; page 23, line 34 to page 25, line 6	1,2,5-8, 10,12
X	US 5 760 246 A (TINO JOSEPH A ET AL) 2 June 1998 (1998-06-02) abstract; example 275 column 53, line 9 - line 32	1,5,8, 10,12
X	EP 0 573 271 A (LILLY CO ELI) 8 December 1993 (1993-12-08) page 5, line 3 - line 7; claims 1,6,8	1,10,12
P,X	WO 00 49037 A (LILLY CO ELI; DODGE JEFFREY ALAN (US); LUGAR CHARLES WILLIS III (U) 24 August 2000 (2000-08-24) claims 1,6	1,2,5,8, 10,12
X	WO 00 21550 A (HARVARD COLLEGE) 20 April 2000 (2000-04-20) page 11, line 7 - line 18; claims 13,14	11,13
A	WO 99 65897 A (RAMURTHY SAVITHRY; CHIRON CORP (US); GOFF DANE (US); NUSS JOHN M () 23 December 1999 (1999-12-23) cited in the application claims 1,73,76,87,88	1,10,12
A,P	EP 1 106 180 A (CT NAT DE) 13 June 2001 (2001-06-13) tables 1,2	10-13

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 11 and 13 relate to a pharmaceutical composition defined by reference to a desirable characteristic or property, namely an inhibitory effect against cdk5. Since claims 11 and 13 are independent claims (without a reference to claim 1, they claim any pharmaceutical composition comprising a cdk5 inhibitor (and optionally a further agent) regardless of the underlying chemical structure. Claims 11 and 13 cover all compositions having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds or compositions. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the products by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to those pharmaceutical compositions which comprise at least one compound as defined in claim 1 or in the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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